IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Kothari and Desai
Application No.: 09/973,226
Art Unit: 1615
Examiner: A. Pulliam

Filed: October 9, 2001
For: FLASH-MELT ORAL DOSAGE FORMULATION

Assistant Commissioner for Patents
Washington, D.C. 20231

Declaration of Mansoor A. Khan R.Ph., Ph.D. Pursuant to 37 C.F.R. §1.132

I, Mansoor A. Khan, R.Ph., Ph.D. do hereby declare as follows:

1. As of the date of this Declaration, I am currently employed as Professor of Pharmaceutics in the School of Pharmacy at Texas Tech University Health Sciences Center, 1300 Coulter Amarillo, TX and was the Founding Director of its Graduate Program in Pharmaceutics.

2. As of June 2004, I will be employed by the United States Food and Drug Administration as the Director of the Division of Product Quality Research in the Office of Therapeutic Testing and Research. The remit of the Division of Product Quality Research includes the development of rational, science-based requirements for drug substances and excipients which are appropriate to a specific quality and performance objective.

3. I have obtained over 25 research grants as principal investigator. I have also published more than 100 peer-reviewed manuscripts, four books and two book-chapters. I have presented more than 100 posters/podia in American Association of Pharmaceutical Scientists and Controlled Release Society Meetings.

4. I am currently an Editorial Advisory Board Member of the Pharmaceutical Technology Journal and the Journal of Clinical Research and Regulatory Affairs. I am also a reviewer for the Pharmaceutical Research, Journal of Pharmaceutical

Sciences, International Journal of Pharmaceutics, Journal of Controlled Release, European Journal of Pharmaceutical Sciences, Journal of Microencapsulation, and AAPSPharmSciTech.

5. I have held several leadership positions in the American Association of Pharmaceutical Scientists, most notably as the Pharmaceutics and Drug Delivery Section Secretary/Treasurer (2001-2004), Pharmaceutical Technologies Section Chair, Program Chair, and General Chair of the Midwest Regional Meetings, Short Course and Workshop Committee Co-Chair, member of the AAPS task force and abstract screening. I have been a symposia moderator, organizer and speaker in several American Association of Pharmaceutical Scientists and other national and regional meetings.

6. I am a registered pharmacist and obtained my B.S. degree in Pharmacy from Kakatiya University, India (1982), M.S. degree in Pharmaceutics from Idaho State University (1988), and Ph.D. degree in Industrial Pharmacy from St. John's University at New York (1992).

7. Prior to joining Texas Tech, I was Associate Professor of Pharmaceutics at the University of Louisiana at Monroe.

8. I teach industrial pharmacy, advanced pharmaceutics, biopharmaceutics and drug delivery courses to graduate and Pharm.D. students. I served as major advisor for one M.S. and ten Ph.D. graduates/students.

9. I was retained by Applicants to review the above-referenced patent application and accompanying office actions, amendments and replies in order to render a professional opinion as to whether WO 98/03064 (hereinafter "Sullivan") is a non-analogous art reference with respect to Applicants' claimed invention.

10. After having reviewed Sullivan, the above-referenced patent application, accompanying Office Actions, Amendments and Replies and having have reviewed the definition of a non-analogous art reference as presented in MPEP§2141.01(a), it is my professional opinion that Sullivan is a non-analogous art reference with respect to Applicants' claimed invention for the reasons set forth below.

11. MPEP §2141.01(a) requires that "[i]n order to rely on a reference as a basis for rejection of an applicant's invention, *the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem* with which the inventor was concerned." (emphasis added). Neither one of these criteria can be satisfied by Sullivan.

12. First, Sullivan is *not* in the field of Applicants' endeavor.

13. Sullivan is in the field of tablets which are intended to disintegrate in the stomach not in the mouth. Applicants' invention is directed to "flashmelt" tablets, *i.e.*, formulations which are designed to melt on the *tongue* with minimal moisture present and which are *not* required to be chewed. Thus, Applicants' flashmelt pharmaceutical formulation are designed to release the drug in the oral cavity, whereas Sullivan teaches a hardened tablet designed to release the drug in the *stomach* or *intestines* only *after* being *swallowed.*

14. As one skilled in the art of pharmaceutical development and having knowledge of both the Applicants' field and Sullivan's field, it is my opinion that no reasonable person skilled in the art of designing flashmelt tablets would be motivated to rely upon the teachings of a reference such as Sullivan which is directed to tablets that are intended to disintegrate in the stomach. In fact, it is my opinion that these art fields would teach *against* each other, not suggest how to improve the other formulation. Sullivan provides actual data to support this. On page 10 columns 16 and 17, Sullivan reveals data showing that in order for its tablets to disintegrate, the tablet must be placed in a large volume of water (1,000 ml), the water must be heated to 37 °C and the water must then be agitated. This test is a standard test used for tablets designed to *delay disintegration* until the drug reaches the stomach of the patient. *See* USP 701 XXII Disintegration Test. Moreover, Sullivan makes no mention of the *minimal* amount of water needed to disintegrate its tablets as do Applicants. After reviewing Sullivan, I did not locate a single instance where it taught or suggested that the formulations disclosed therein would rapidly dissolve on the tongue of a patient. That is because the scope of Sullivan's invention is tablets that are intended to be swallowed and disintegrate in the stomach *not* in the mouth. In fact, if one of

Sullivan's tablets were t dissolve on the tongue when it was not intended to do so, it would compromise the efficacy and/or safety of the drug because is very likely that the patient would eject the tablet because of the bitter taste often associated with active ingredients.

15. Moreover, Sullivan defines its field distinct from Applicants by stating "representative of earlier *efforts in this field* are, for example U.S. Patent 4,744,987 (Mehra et al), directed to a blend of microcrystalline cellulose (MCC) and calcium carbonate in pharmaceuticals; PCT publication WO 92/12633 (Mehra et al.), which discloses a combination of MCC and a nitrogenous compound; and Japanese Application 81/022,839 (Japan Metals and Chemical Co.) which employs a disintegrant comprising bentonite and an alkali metal silicate for agricultural formulations." (emphasis added) *See* Sullivan 2:4-10. These references are *not* in the field of flashmelt pharmaceutical tablets.

16. Second, the "particular problems" to be solved between Sullivan and Applicants' invention are very different.

17. Sullivan's goal is not simply to achieve more rapid disintegration for that admittedly was accomplished by the more costly superdisintegrants discussed by Sullivan in its Background Section. *See* Sullivan 1:20-25. Sullivan's "problem" was reducing high cost solid tablets requiring expensive superdisintegrants to allow the tablet to disintegrate within a given time in the *stomach*. *See* Sullivan 2:15-30. The "problem" Applicants solved was creating a tablet that would melt on the *tongue* and which could be manufactured by a process known as "direct compression." The problems solved by each invention are very different and thus the second criteria of MPEP §2141.01(a) is not satisfied either.

18. Therefore, since neither of the criteria under MPEP §2141.01(a) can be satisfied, it is my opinion that Sullivan is not an an analogous art reference.

I hereby declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Dated this 19th day of April 2004

Mansoor A. Khan, R.Ph., Ph.D.